Exhibit B

International Journal of the Medical Council on Alcohol

OXFORD UNIVERSITY PRESS

ALCOHOL AND ALCOHOLISM

Volume 36 Number 6 November/December 2001

CONTENTS

Please visit the journal's World Wide Web site at http://alcalc.oupjournals.org/

Printed in Great Britain by Hobbs the Printers Ltd, Brunel Road, Totton, Hampshire SO40 3WX

Alcohol & Alcoholism Vol. 36, No. 6, pp. 553–555, 2001

A CASE OF KORSAKOFF'S SYNDROME IMPROVED BY HIGH DOSES OF DONEPEZIL

JUN-ICHI IGA*, MAKOTO ARAKI, YASUHITO ISHIMOTO and TETSURO OHMORI

Department of Neuropsychiatry, University of Tokushima School of Medicine, 3-18-15 Kuramoto-Cho, Tokushima-Shi-770 8503, Japan

(*Received* 14 *February* 2001; *in revised form* 9 *April* 2001; *accepted* 21 *May* 2001)

Abstract — We present a case of Korsakoff's syndrome that was successfully treated with high doses of donepezil, an inhibitor of acetylcholine esterase, known to retard the progress of symptoms in Alzheimer's disease. The patient was a 46-year-old married Japanese woman who began to drink alcohol after she married. After several years of drinking she developed typical symptoms of the Korsakoff syndrome. Donepezil was started after treatment with thiamine or thiamine plus fluvoxamine had failed. Her amnestic symptoms as well as her quality of life improved markedly during donepezil treatment. Inhibition of acetylcholine esterase may be an effective treatment for Korsakoff's syndrome.

INTRODUCTION

Korsakoff's syndrome is permanent in at least a partial form in perhaps 80% of patients (Davis *et al.*, 1971). The noradrenergic, serotonergic and cholinergic systems have all been implicated in the physiological pathway of the Korsakoff syndrome (McEntee and Mair, 1990). It has been reported that fluvoxamine (Martin *et al.*, 1995) and clonidine (McEntee and Mair, 1980; Mair and McEntee, 1986) both improve the Korsakoff state. In this paper, we present a case of Korsakoff's syndrome that was successfully treated with high doses of donepezil, an inhibitor of acetylcholine esterase, known to retard the symptoms of Alzheimer's disease. There are also reports that donepezil improves memory disturbances due to traumatic brain injury (Taverni *et al.*, 1998; Whitlock, 1999), dementia with Levy bodies (Shea *et al.*, 1998) and vascular dementia (Mendez *et al.*, 1999), but, as far as we could ascertain from an English-language literature search using Pub Med, this is the first report showing the therapeutic effect of the drug in the Korsakoff syndrome.

CASE REPORT

'Ms A' was a 46-year-old married Japanese woman. She finished a 2-year training course after graduating from Junior High School. She had worked in a petrol station, a hardware shop and a Chinese restaurant. She began to drink occasionally after she married at the age of 23 years, and gave birth to a baby at the age of 36, when she left her job and became a housewife. When she was 40 years of age, she and her family moved to an unfamiliar area in the country, after which she often felt frustrated with just looking after her child and with her social environment, and the amount of alcohol she was drinking increased during this time.

In March 2000, her husband noticed that she was not eating at all. She was hospitalized because of dehydration and weakness. The patient's physical condition improved following rehydration, but her craving for alcohol, her inappropriate behaviour, as well as her severe memory disturbance were noted. She was transferred to the Department of Psychiatry at the University Hospital of Tokushima 12 days later.

On admission to the University Hospital, a marked retrograde memory loss of about 10 years was observed. The patient claimed to be younger than she really was and denied giving birth to, and caring for, her child, insisting that the child belonged to her elder sister. There was also a marked disturbance of recent memory, disorientation, confabulation, and an indifferent attitude. Neurological examination revealed nystagmus in the right and left gaze, difficulty in standing on one foot bilaterally but no disturbance of co-ordination. Physical examination showed peri-oral erythemas, slight abdominal distention and bilateral pretibial oedema. There was no abnormality of electrocardiogram, electroencephalogram, brain computed tomography or magnetic resonance imaging scans. There was a slight rise of aspartate aminotransferase, alanine aminotransferase, pancytopenia, and low serum albumin levels. The physicians diagnosed compensated cirrhosis and oesophageal varices.

The patient was treated with peroral vitamins (thiamine 200 mg, pyridoxine 200 mg and cyanocobalamin 2 mg/day) from admission and until day 210. Her nystagmus and gait disturbance improved within a week, but the amnesia, disorientation and confabulation did not improve. She complained that her money had been stolen and her belongings were broken and she sometimes quarrelled with other patients. The patient could not take care of her own needs adequately and required constant nursing care.

The patient was given 25 mg/day of fluvoxamine in addition to the vitamin preparation, starting 21 days after admission to the University Hospital (day 21). Fluvoxamine was gradually increased up to 200 mg/day over the next 3 weeks and continued until day 56 without any improvement and was therefore discontinued. A 3 mg/day dose of donepezil was started 7 days later (day 63) and the dosage of donepezil was gradually increased to 15 mg/day. The patient's clinical symptoms were evaluated using the revised Hasegawa dementia scale (HDS-R) (Hasegawa, 1983) and a mini-mental state examination (MMSE) (Folstein *et al.*, 1975) was carried out every week (Fig. 1). The patient did not remember the last examination at all. Thirty-five days later (day 97), she developed insight into her memory disturbance and began to cry when she realized her inability to remember. Her memory

*Author to whom correspondence should be addressed.

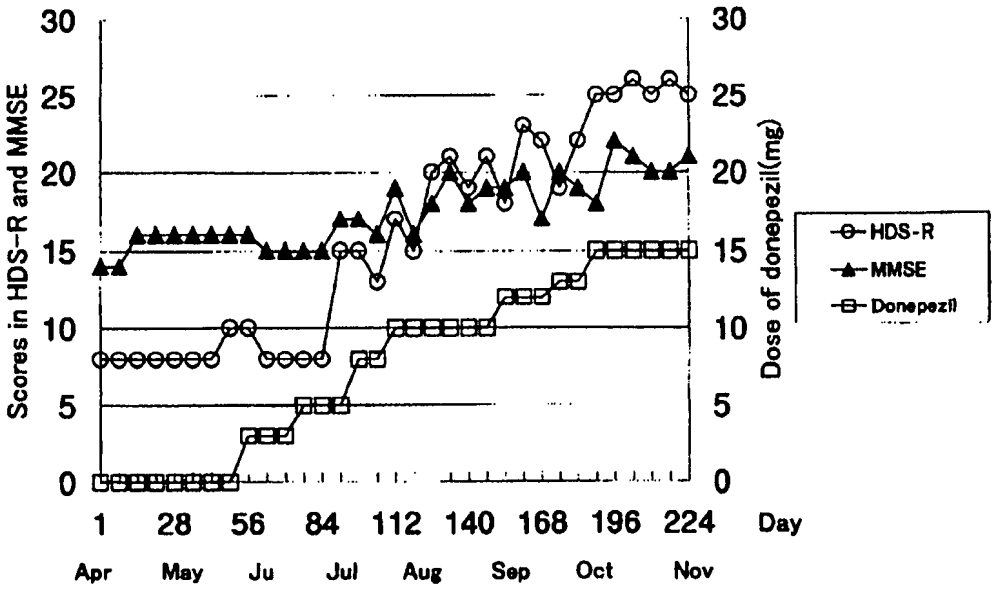

Fig. 1. Revised Hasegawa dementia scale (HDS-R) and mini-mental state examination (MMSE) scores, before and during donepezil treatment. Donepezil improved HDS-R from 8 to 26 and MMSE from 15 to 22.

gradually improved and she remembered her child. She was often seen reading newspapers and magazines. The changes of scores of HDS-R and MMSE are shown in Fig. 1. The nurses' rating scores (KOMI chart) (Hitoe, 1996) for cognitive and behavioural aspects of daily life were 12/75 and 16/75 respectively on admission. The score of cognition and behaviour improved to 56/75 and 47/75 respectively by the end of November 2000 (i.e. on day 231).

Before initiating treatment, we explained to her family the possible effects and side-effects of donepezil and obtained their consent to proceed and publish this case report. In fact no side-effects were observed during treatment.

DISCUSSION

To our knowledge, this is the first report showing that donepezil is effective in the treatment of the Korsakoff syndrome. The patient was treated with 200 mg/day of peroral thiamine for 21 days without improvement. She was then treated with thiamine plus fluvoxamine for about 35 days (until day 56) but no improvement was seen, contrary to previous reports (Martin *et al.*, 1995). Her symptoms only began to show improvement after donepezil was prescribed. Donepezil improved the HDS-R score from 8 to 26 and the MMSE from 15 to 22. These increased scores were not due to the learning effect after repeated measurements, since the patient did not remember having taken the test the previous week. Moreover, as shown in the change in the nurses' scores for cognitive and behavioural aspects of daily life, the quality of life improved greatly with the improvement of the HRS-R and MMSE scores. The dosage of donepezil was increased to 15 mg and this dosage is thought to exert the maximum effect on the inhibition of choline esterase (Rogers *et al.*, 1998).

Cholinergic involvement in Korsakoff's syndrome has been suggested. Mayes *et al.* (1988) made morphometric measurements of cholinergic nuclei in the basal forebrains of two cases of Korsakoff's syndrome, the patients having been psychometrically tested while alive and their diagnoses confirmed at post-mortem. In both cases, the post-mortem study showed a decrease in the number or nucleolar volume of magnocellular neurons in the nucleus basalis of Meynert, the major source of cortical acetylcholine. It has also been reported that thiamine deficiency may damage the cholinergic system as a result of a complex interaction between cellular, neurochemical and metabolic properties (Witt, 1985). Moreover, it is reported that cholinergic-rich brain transplants or cholinergic drugs reverse alcohol-induced memory deficits in animals (Arendt *et al.*, 1988; Hodges *et al.*, 1991). Donepezil may improve the amnestic symptoms by activating the cholinergic transmission from the basal forebrain to the cortex. Larger trials are needed to substantiate the safety and efficacy of donepezil for treatment of memory impairment of Korsakoff syndrome.

REFERENCES

Arendt, T., Allen, Y., Sinden, J., Schugens, M. M., Marchbanks, R. M., Lantos, P. L. and Gray, J. A. (1988) Cholinergic-rich brain transplants reverse alcohol-induced memory deficits. *Nature* 332, 448–450.

Davis, V. M., Adams, R. D. and Collins, G. H. (1971) The Wernicke–Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. *Contemporary Neurology Series* **7**, 1–206.

Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975) 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12**, 189–198.

Hasegawa, K. (1983) The clinical assessment of dementia in the aged: a dementia screening scale for psycho geriatric patients. In *Aging in the Eighties and Beyond*, Bergener, M. *et al.* eds, pp. 207–218. Springer, New York.

Hitoe K. (1996) *KOMI Chart: A Method for Practice of Nursing and Care*. (In Japanese.) Gendaisya, Tokyo.

Hodges, H., Allen, Y., Sinden, J., Mitchell, S. N., Arendt, T., Lantos, P. L. and Gray, J. A. (1991) The effects of cholinergic drugs and cholinergic-rich foetal neural transplants on alcohol-induced deficits in radial maze performance in rat. *Behavioural Brain Research* **43**, 7–28.

Mair, R. G. and McEntee, W. J. (1986) Cognitive enhancement in Korsakoff's psychosis by clonidine: a comparison with L-dopa and ephedrine. *Psychopharmacology* **88**, 274–280.

Martin, P. R., Adinoff, B., Lane, E., Stapleton, J. M., Bone, G. A. H., Weingartner, H., Linnoila, M. and Eckardt, M. J. (1995) Fluvoxamine treatment of alcoholic amnestic disorder. *European Neuropsychopharmacology* **5**, 27–33.

Mayes, A. R., Meudell, P. R., Mann, D. and Pickering, A. (1988) Location of lesions in Korsakoff's syndrome: neuropsychological and neuropathological data on two patients. *Cortex* **24**, 367–388.

McEntee, W. J. and Mair, R. G. (1980) Memory enhancement in Korsakoff's psychosis by clonidine: further evidence for a noradrenergic deficit. *Annals of Neurology* **7**, 466–470.

McEntee, W. J. and Mair, R. G. (1990) The Korsakoff syndrome: a neurochemical perspective. *Trends in Neurosciences* **13**, 340–344.

Mendez, M. F., Younesi, F. L. and Perryman, K. M. (1999) Use of donepezil for vascular dementia: preliminary clinical experience. *Journal of Neuropsychiatry and Clinical Neurosciences* **11**, 268–270.

Rogers, S. L., Farlow, M. R., Doody, R. S., Mohs, R. and Friedhoff, L. T. (1998) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology* **50**, 136–145.

Shea, C., MacKnight, C. and Rockwood, K. (1998) Donepezil for treatment of dementia with Levy Bodies: a case series of nine patients. *International Psychogeriatrics* **10**, 229–238.

Taverni, J. P., Seliger, G. and Lichtman, S. W. (1998) Donepezil medicated memory improvement in traumatic brain injury during post acute rehabilitation. *Brain Injury* **12**, 77–80.

Whitlock, Jr, J. A. (1999) Brain injury, cognitive impairment, and donepezil. *Journal of Head Trauma and Rehabilitation* **14**, 424–427.

Witt, E. D. (1985) Neuroanatomical consequences of thiamine deficiency: a comparative analysis. *Alcohol and Alcoholism* **20**, 201–221.